REMARKS

An Office Action was mailed in the above-captioned application on December 29, 2003. In such Office Action claims 3-5 were pending. Claims 3-5 were rejected. This Amendment and Remarks document is submitted in response to said Office Action.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 3-5 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The first paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A 1971). Applicant notes that while the Examiner has made an enablement rejection, the Examiner's language is consistent with a written description rejection in some instances. Applicant's remarks are therefore directed to the Examiner's language, with emphasis on the appropriate statutory provision.

Claim 3. Claim 3 is drawn to a pharmaceutical composition for treatment of deep vein thrombosis (DVT) comprising a nucleic acid ligand to a β_3 integrin and a pharmaceutically acceptable excipient. The Examiner has asserted that the treating of DVT with any ligand of β_3 is not taught, the specification fails to teach how to treat DVT, the level of predictability in the art of treating DVT is low, no working examples are provided, and undue experimentation would be required to treat DVT. Applicant does not acquiesce in the Examiner's reasoning with regard to Claim 3; however, solely in the interest of expediting prosecution, Claim 3 has been cancelled. Applicant reserves the right to prosecute the subject matter of Claim 3 in a continuing application.

Claim 4. Claim 4 is directed to a method for detecting DVT comprising providing a nucleic acid ligand to a β_3 integrin, said nucleic acid ligand to a β_3 integrin being conjugated to a radioactive label, administering said nucleic acid ligand to an individual, and detecting the site of said thrombosis by analyzing the localization of said nucleic acid ligand using a radioimaging technique. The Examiner asserts that the specification provides no teaching of detecting DVT , the level of predictability in detecting DVT is low, the specification provides no examples of detecting DVT in an individual, but merely teaches the localization of one aptamer to an induced clot in a rabbit, and undue experimentation would be required to detect DVT.

Applicant respectfully traverses this rejection. The specification and prior art provide evidence of a correlation between binding to β_3 integrin and detecting DVT in individuals.

Detecting thrombus formation, including DVT, with a radiolabeled β_3-binding agent is well-known in the art. Reports of thrombus detection, including DVT detection, using radiolabeled fibrinogen (which binds to $\alpha_{IIb}\beta_3$) date back to at least the mid-1970s. (*See* Harwig, et al., *In Vivo* Behavior of 99mTc-Fibrinogen and its Potential as a Thrombus-Imaging Agent, *J Nucl Med.* 1976 Jan;17(1):40-6; and Jonckheer, et al, The Interpretation of Phlebograms Using Fibrinogen Labeled with 99 mTc, *Eur J Nucl Med.* 1978;3(4):233-8 (abstracts enclosed)). Numerous additional reports of radiolabel-mediated detection of thrombi can be found in this time period (*e.g.*, a search in MEDLINE for "dvt imaging 99mtc" from 1980-1989 returns 40 reports.) More recent reports describe radioimaging of thrombi with $\alpha_{IIb}\beta_3$ (also referred to as GPIIbIIIa) antagonists. (*See*, *e.g.*, Barrett, et al., Biological Evaluation of Thrombus Imaging Agents Utilizing Water Soluble Phosphines and Tricine as Coligands When Used to Label a Hydrazinonicotinamide-Modified Cyclic Glycoprotein IIb/IIIa Receptor Antagonist with 99mTc, *Bioconjug Chem.* 1997 Mar-Apr;8(2):155-60; and Mousa, et al., Novel Technetium-99m-labeled Platelet GPIIb/IIIa Receptor Antagonists as Potential Imaging Agents for Venous and Arterial Thrombosis, *Coron Artery Dis.* 1998;9(2-3):131-41 (abstracts enclosed)). The prior art clearly supports a correlation between β_3-binding molecules and the ability to detect thrombi, including DVT.

Furthermore, the illustrative examples provided in the specification teach a method of making and using a β_3 integrin nucleic acid ligand to bind to β_3. Furthermore, these working examples provide the necessary guidance for the steps necessary in order to recognize or identify any binding to β_3 by a β_3 nucleic acid ligand in conditions or diseases mediated by β_3. It has

been determined by the courts that no working examples are required to enable a patent application. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Applicant, however, provides a specific *in vivo* Example, Example 6, which indicates the specificity and efficacy of the ligands in the claimed method in a model system. A rigorous or an invariable exact correlation between an *in vivo* or *in vitro* model and the claimed method is not required, rather, only a reasonable correlation is necessary.

The Examiner implies that the rabbit model is not satisfactory for studying human disorders. Applicant asserts that the rabbit animal model is appropriate, and reasonably correlates to the claimed method, meeting the criteria for enablement. On the basis of animal studies, and controlled testing in a limited number of humans (Phase I testing) the Food and Drug Administration may authorize Phase II clinical studies; however, FDA approval is not a prerequisite for finding a compound patentable within the meaning of the patent laws. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2D (BNA) 1115, 1120 (Fed. Cir. 1994). Applicants are not required to demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. MPEP § 2107(III) and cases cited therein.

A specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. In addition, even in an unpredictable art, it is unnecessary to disclose examples for each claimed species. *In re Angstadt*, 537 F.2d 498, 502 (CCPA 1976).

While some experimentation may be necessary to develop specific experimental protocols for imaging DVT with ligands to β_3, such experimentation is not undue, but rather routine in the art (see enclosed abstracts).

Thus, the knowledge available to one of skill in the art, taken together with the disclosure provided regarding radioimaging of DVT with an exemplary β_3 ligand, is sufficient to enable one of skill in the art to perform the claimed methods of detecting DVT.

Claim 5. Claim 5 claims an anti-clotting composition for use in acute coronary syndromes and percutaneous coronary invtervention, the composition comprising a nucleic acid ligand to a β_3 integrin and a pharmaceutically acceptable excipient. The Examiner asserts that anti-clotting composition with any ligand of β_3 is not taught, the specification fails to teach anti-clotting applications, the level of predictability in the anti-clotting art is low, no working examples are provided, and undue experimentation would be required to develop an anti-clotting agent.

Applicant respectfully traverses this rejection. The specification and prior art provide evidence of a correlation between binding to β_3 integrin and anti-clotting applications.

The specification explains that $\alpha_{IIb}\beta_3$ is the major integrin on the surface of platelets where it mediates the adhesion of activated platelets to the plasma protein fibrinogen, and that during clot formation, fibrinogen dimers cross-link platelets to one another through the integrin receptor. Activation of platelets by ADP, epinephrine, collagen or thrombin leads to a dramatic enhancement in integrin ligand binding activity. (Specification, page 6, lines 1-20). The specification further provides examples of $\alpha_{IIb}\beta_3$-binding molecules which are approved anti-clotting drugs, Aggrastat, Integrilin, and ReoPro. These drugs are approved for acute coronary syndrome and/or in patients who are undergoing percutaneous coronary intervention; that is, indications where thrombus (clot) formation is suspected or is likely. (Specification, page 6, lines 21-30). The prior art clearly supports a correlation between β_3-binding molecules, binding to activated platelets, and anti-clotting activity.

Furthermore, the illustrative examples provided in the specification teach a method of making and using a β_3 integrin nucleic acid ligand to bind to activated platelets in Example 5. As explained above, a rigorous or an invariable exact correlation between an *in vivo* or *in vitro* model and the claimed method is not required, rather, only a reasonable correlation is necessary. That is, the specification may be enabling even though some experimentation is necessary, as long as a reasonable amount of guidance is provided with respect to the direction in which the experimentation should proceed. Additionally, it is unnecessary to disclose examples for each claimed species. While some experimentation may be necessary to develop specific anti-clotting compositions comprising ligands to β_3, such experimentation is not undue, but rather routine in the art, as evidenced by the existence of the numerous approved anti-clotting drugs, Aggrastat, Integrilin, and ReoPro, which bind to $\alpha_{IIb}\beta_3$ on activated platelets.

Thus, the knowledge available to one of skill in the art, taken together with the disclosure provided regarding binding to activated platelets with an exemplary β_3 ligand, is sufficient to enable one of skill in the art to prepare the claimed anti-clotting composition.

Reconsideration is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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Darla G. Yoerg, #48,053
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80129
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

Enclosures

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